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Case reports/Kazuistyka

Rasburicase in the treatment of acute kidney injury in a boy with non-malignancy hyperuricemia

Zastosowanie rasburikazy w leczeniu ostrego uszkodzenia nerek u chłopca z hiperurykemią pochodzenia nienowotworowego

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ABSTRACT

In the manuscript authors describe the application of rasburicase in the treatment of acute kidney injury in a child with non-malignancy associated hyperuricemia and combined congenital abnormalities. Rasburicase application was safe, well tolerated and rapidly effective. The significant fall in serum uric acid levels was accompanied by rising diuresis. The improvement of renal function prevented the need for dialysis, which was favorable for the patient and markedly reduced the costs of treatment. Rasburicase could be an option in the treatment of acute kidney injury also in children with marked hyperuricemia of non-malignancy origin.

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Introduction

Hyperuricemia plays an important role in the pathogenesis of acute and chronic diseases including gout, tumor lysis syndrome (TLS), arterial hypertension, renal failure, coronary heart disease, left ventricular hypertrophy and metabolic syndrome [1]. In acute kidney injury (AKI), when the urine flow is low and pH is acidic, uric acid as the substance poorly soluble in water precipitates into crystals in renal tubules. This results in increased risk of tubular obstruction. Additionally hyperuricemia is the cause of enhanced synthesis of reactive oxygen species, renin–angiotensin–aldosterone system activation, increased endothelin-1 production and nitric oxide system inhibition, which contributes to the pathogenesis of AKI [2]. Rasburicase (recombinant urate oxidase) is an efficient protease in urate depletion, which plays a valuable role in the treatment of malignancy – associated TLS [3]. Its action includes uric acid (UA) conversion to more soluble allantoin. This drug does not cause the accumulation of intermediate products of purine metabolism pathway such as xanthine. Intraluminal obstruction of renal tubules by precipitating uric acid has been avoided [4].

Urate oxidase was produced from cultures of *Aspergillus flavus*. It was introduced to the treatment of TLS in Europe in 1974. Now it is used as the recombinant form – rasburicase – Fasturtec (Sanofi-Aventis, Paris, France). The usage of rasburicase has eliminated serious immunological complications caused by non-recombinant compound [5].

There is not much data in literature on rasburicase usage in AKI in children [4]. In this manuscript authors describe the application of rasburicase in the treatment of AKI in a child with acute non-malignancy associated hyperuricemia and combined congenital abnormalities.

Case report

A 5-year-old boy was admitted to pediatric department with a 4-day history of vomiting, dehydration and oliguria in the course of gastro-intestinal infection. Past history was remarkable. He had multiply congenital malformations [face dysmorphism and limb deformation with muscular contractures, hypostature, organic heart disease – significant mitral insufficiency (+ + +) with ventricular septal defect, corneal and scleral staphylomas, amaurotic right bulb, congenital cataract of left eye].

He suffered from AKI 10 months prior to current hospitalization. He developed multiorgan dysfunction syndrome after the reimplantation of artificial mitral valve. He required dialysis for 11 days (2 days on peritoneal dialysis, 9 days on continuous hemodiafiltration). At the age of 3 he had cerebral stroke due to thrombosis of right middle cerebral artery. From the age of 4 he had tracheostomy. Additionally boy received antihypertensive medication, anticoagulant (acenocumarol) for cardiological purposes, he also continued antiepileptic treatment.

On admission he was pale, fatigued with marked dyspnoe. On examination artificial right eye bulb (after the rupture of congenitally deformed bulb), dry oral cavity mucosa, dry skin, red throat, postoperative scar in sternal area, additionally

were found. No signs of cardiovascular insufficiency were noted. He remained in sitting position on a wheel chair. His intellectual development was slightly delayed.

Laboratory test values showed anemia (Hb: 9.6 g/dl), high platelet count (595 G/L), high leukocyte count (15.2 G/L), metabolic acidosis (HCO_3^- 6.3 mmol/L), hyperuricemia (675 $\mu\text{mol/L}$), hyponatremia (130 mmol/L), hypoproteinemia (50.2 g/L), hypoalbuminemia (21.2 g/L), higher creatinine (84 $\mu\text{mol/L}$) and urea values (11.7 mmol/L), high CRP concentration (79.3 mg/L), high grade proteinuria (3.6–14.0–27.0 g/L) without the features of nephrotic syndrome. Prothrombin time (28.3 s), INR: 2.6 and APTT (46.2 s) were prolonged. The chest X-ray revealed bilateral pneumonia. Echocardiographic examination confirmed artificial mitral valve with maximum gradient 20 mmHg and tricuspid valve insufficiency with pulmonary hypertension (maximum gradient 60–70 mmHg). Extrarenal cause of AKI was excluded. On ultrasound typically localized kidneys with mean length of 10 cm, blurred image and increased cortex echogenicity were shown.

Conservative treatment of AKI was administered with no significant improvement. General edema persisted and hyperuricemia worsened. On day 4th rasburicase was applied at the dose 0.1 mg/kg body weight. Daily urine output and values of selected laboratory parameters on consecutive days are shown in Fig. 1.

UA concentration significantly dropped during first 24 h after rasburicase administration and reached normal values. On day 12 furosemide and dopamine were withdrawn. Renal replacement therapy was not implemented. Creatinine and urea values normalized at day 14. Alkalosis persisted from day 5 without supplementation. The increase of serum potassium concentration and the decrease of calcium were noted as shown on Fig. 1e and f.

The treatment of pneumonia was finished at day 20 and the boy has been discharged. He remained under the strict nephrological control in out-patient clinic. Mild hyperuricemia was present during the time of further observation and was rather caused by chronic kidney disease than inherited defect of purine metabolism. Kidney function gradually deteriorated to reach the stadium 5 of chronic kidney disease after the 2.5 years from the episode of acute kidney injury.

Discussion

The conservative management of hyperuricaemia involves the use of allopurinol, high-volume hydration, diuretic therapy and urine alkalinization. In patients with anuria or oliguria this method is not effective [6].

Studies mostly in TLS patients confirmed that rasburicase application is safe, well tolerated and rapidly effective (onset is present already after 4 h) [3]. The dramatic fall in serum UA levels is accompanied by rising diuresis. This prevents the need for dialysis among TLS patients, which is favorable and markedly reduces the costs of treatment. Hummel et al. [7] gave low rasburicase doses in oncological patients, starting from 0.049 mg/kg/24 h and after that adjusting the dose to UA level with excellent effect. Rasburicase has been proven to dissolve tubular uric acid crystals. Segura et al. [8] postulated that rasburicase can also act in urinary tract, fragmentizing

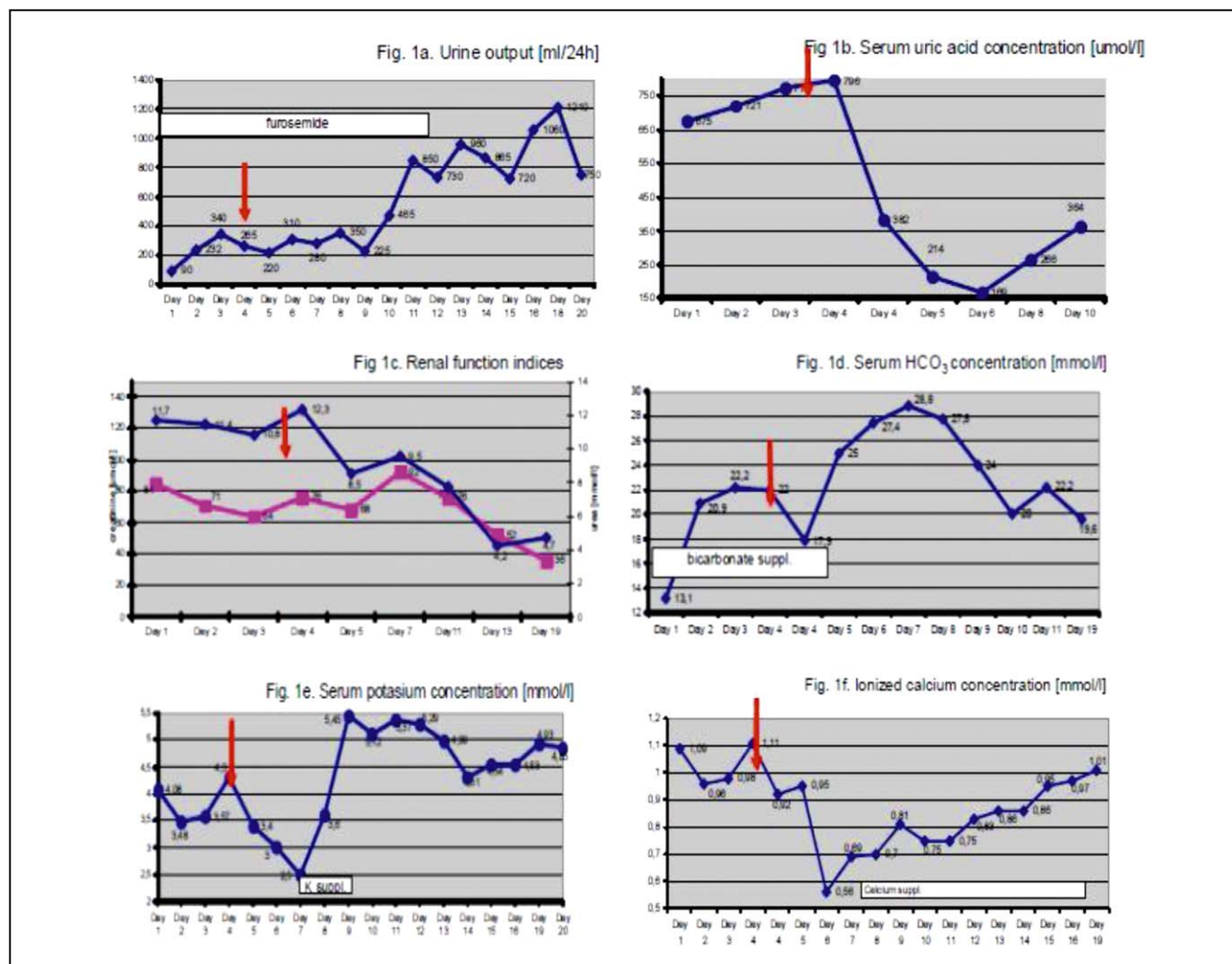


Fig. 1 – Daily urine output and values of selected laboratory parameters on consecutive days; a – daily urine output, b – uric acid concentration, c – renal function indices, d – bicarbonate concentration, e – potassium concentration, f – ionized calcium concentration; red arrow – rasburicase bolus

Ryc. 1 – Dobowa diureza i wartości wybranych parametrów laboratoryjnych w czasie hospitalizacji; a – dobowe wydalenie moczu, b – stężenie kwasu moczowego, c – wskaźniki funkcji nerek, d – stężenie wodorowęglanu, e – stężenie potasu, F – stężenie wapnia zjonizowanego; czerwona strzałka – bolus rasburikazy

renal calculi, promoting relief of obstructive uropathy. They applied successfully rasburicase in 2 adults with acute obstructive nephropathy from renal calculi. De Angelis et al. [1] showed that after 7 days of the rasburicase more pronounced antihyperuricemic effect was obtained in men than in women with renal failure.

In our boy with AKI we considered the use of rasburicase because of excessively elevated UA serum levels not resolving after conservative management and to control volume of infused fluids and manage effective diuresis (Fig. 1c). Boy had cardiological complications – organic heart abnormality with pulmonary hypertension – and in his past history suffered cerebral stroke and artificial mitral valve thrombosis.

The instillation of hemodialysis carried higher risk, and as he had peritoneal dialysis and peritoneal drainage after cardiac surgery before, so we could expect the possibility of

peritoneal adhesions. The treatment with one low-dose rasburicase (0.1 mg/kg body weight) was very efficient and prevented dialysis. Significant decline of UA serum levels (Fig. 1a) and normalization of renal indices (Fig. 1b) have been observed accompanied by metabolic alkalosis (Fig. 1d), hypokalemia (Fig. 1e), and hypocalcemia (Fig. 1f). Metabolic alterations after the use of rasburicase required potassium and calcium supplementation (risk of epileptic event).

In line with our observations other authors shown that alkalinization could be withheld using rasburicase [6]. Other effects of rasburicase include calcium phosphate tissue deposition caused by excessive phosphate reabsorption. Góth [9] described increased production and high concentration of hydrogen peroxide during rasburicase treatment. This could cause hemolysis and methemoglobin formation, in case of glucose-6-phosphate-dehydrogenase and catalase deficiencies.

Roncal et al. [10] described in rats, that treatment with rasburicase reversed the inflammatory changes and lessened tubular injury with an improvement in renal function.

During the prolonged treatment antibodies against rasburicase have been detected in serum of patients. These antibodies declined the treatment efficiency. It is hypothesized that UA might be directly involved in the apoptotic process. Hobbs et al. treated infants with AKI with rasburicase. They report beneficial effect on lowering serum UA concentration. The side effects of such treatment were absent [11].

In conclusion, rasburicase could be an option in the treatment of AKI with marked hyperuricemia of non-malignancy origin in children.

Authors' contributions/Wkład autorów

Maria Szczepanska – study design, data interpretation, Literature Search, Piotr Adamczyk – data collection, literature search, Katarzyna Ziora – data interpretation, acceptance of final manuscript version, Tomasz Szczepański – acceptance of final manuscript version.

Conflict of interest/Konflikt interesu

None declared.

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